**Title: Elucidating the function of the transmembrane protein gene *TMEM244* and its role in the development of lymphoid malignancies**

The civilization progress and the progress of medical sciences have led to a considerable prolongation of human life. At the same time a drastic decrease in population growth has led to an increase in the proportion of elderly people in the society. The risk of cancer increases with age, therefore in an aging society we observe a steady increase in the incidence of cancer. Unfortunately, despite significant progress in treatment, cancer mortality is still rising. In Poland cancer is the second cause of death after cardiovascular disease, but in some countries it is already the main cause. Tumors, that were once rare, are more common now. T-cell lymphomas, including Sézary's syndrome, are rare tumors, that are developed mainly in elderly people, whose incidence has increased threefold over the last quarter century.

Named after Albert Sézary, a physician who first described this disease, Sézary syndrome develops from the skin helper T cells. The disease is characterized by the erythroderma, accompanied by a very strong pruritus and enlarged lymph nodes, liver and spleen. The characteristic, malignant T cells, called Sézary cells, are detected in the blood. The disease has an aggressive course and is incurable, with an average survival of about 3 years. Despite numerous cytogenetic and molecular studies, which have shown a great number of genome damage in tumor cells, the pathogenesis of Sézary syndrome remains unknown. The reason for this is the huge variety in chromosomal changes and DNA mutations among individual patients. As a result, it is difficult to distinguish changes that caused the disease, from those that arose during disease progression.

During our previous project we performed the whole genome and transcriptome next generation sequencing (NGS) of Sézary cells and we discovered the expression of gene *TMEM244*, encoding a transmembrane protein. Expression of *TMEM244* was detected in all Sézary syndrome patients but not in normal T cells (CD3+) from healthy donors. Those results were confirmed by quantitative real time PCR performed for new SS cases and control group of normal helper T cells (CD3+/CD4+) and mononuclear cells form healthy donors. So far the role of *TMEM244* is unknown and our publication is the only one concerning this gene.

The purpose of this project is to find the biological function of *TMEM244* and establish its role in development of SS. Our research hypothesis assumes that, as a result of TMEM244 appearance in the membrane of Sézary cells, a new signaling pathway is switched on, that is not present in normal lymphoid cells. The activation of this pathway gives Sézary cells a constant signal for proliferation. In time, constantly dividing cells acquire more and more genetic changes, leading to inhibition of the programmed cell death (apoptosis), immortalization, and resulting in malignant transformation. Moreover, we plan to check whether *TMEM244* is expressed in other lymphoid malignancies. Using genetic engineering (siRNA, lentiviral expression vectors) we will study the effect of induction of *TMEM244* expression in normal T cells, where it is not expressed. We will also knockout this gene in primary malignant Sézary cells and Sézary syndrome cell line with *TMEM244* expression, what will help us to understand the biological function of our gene of interest. Next, we will use modern, proteomic techniques, like co-immunoprecipitation and advanced mass spectrometry (MALDI-TOF MS), to identify proteins that are bound to TMEM244 and establish the nature of their interactions and mechanisms of action.

In addition to the pioneering description of the biological function of the *TMEM244* gene, the discovery of its contribution to the development of Sézary syndrome and maybe other lymphoid tumors, will allow us to better understand the pathogenesis of these diseases and, in the future, to develop drugs specifically affecting the gene or protein TMEM244. The high specificity of *TMEM244* expression might be used in the diagnosis of lymphoid tumors, which often cause diagnostic problems, due to the macroscopic and microscopic similarity to reactive lymphoid infiltrates.